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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/759,037	01/20/2004	Yosef Shaul	27169	7306

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EXAMINER	
HILL, MYRON G	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 12/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/759,037	SHAUL ET AL.	
	Examiner	Art Unit	
	Myron G. Hill	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/17/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election without traverse of SEQ ID# 4, in paper filed July 28, 2004 is acknowledged.

Election was made **without** traverse.

Claims 1- 8 are under consideration.

Information Disclosure Statement

A signed and initialed copy of the IDS paper filed June 17, 2004 is enclosed.

Priority

Applicant has included a priority claim in the first line of the specification to US 09/409,096, now US 6589534, filed September 30, 1999.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1- 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention. The method lacks a conclusion step which indicates that inhibiting has occurred and indicates how inhibition is determined or what the result is.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1- 8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID# 4 binding to a portion of HBV preS1 (as defined by SEQ ID# 8 and 9), does not reasonably provide enablement for in vivo activity, prevention of disease, and 60% homologous regions, portions, or whole SEQID# 4 that function to inhibit attachment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). They include: (1) the nature of the invention, (2) the state of the prior art, (3) the presence or absence of working examples, (4) the amount or direction or guidance presented, (5) the quantity of experimentation necessary, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The invention is drawn to inhibiting attachment of HBV to hepatic cells by exposing the cells to a urine derived protein of SEQ ID# 4 or 60% homologous to it or portions of it.

The prior art teaches that antibodies to the same region of HBV sAg preS1 are neutralizing for HBV infectivity (Neurath *et al.* Nature from IDS).

The specification teaches that this protein was discovered by screening urine for proteins that bind SEQ ID# 8 or 9. The specification analyzes the protein and determines the physical properties of the protein.

The presence or absence of working examples. The specification does not provide any working examples that would indicate the claimed method is able to be administered to an animal in such a way that they will be effective at inhibiting attachment of HBV to hepatic cells.

The amount or direction or guidance presented. The specification provides evidence under *in vitro* experimental conditions that SEQ ID #4 binds to the preS region included in SEQ ID#s 8 and 9. The specification does not teach how the pharmaceutical composition is administered in such a way as to function.

It would require undue experimentation to practice the invention as claimed.

The specification does not provide sufficient guidance to allow one skilled in the art to use the claimed method to inhibit the binding of HBV to hepatic cells *in vivo*. The specification does not provide teachings to establish effective dosages or methods of administration of the pharmaceutical composition. The specification does not provide any teaching as to how to administer the pharmaceutical composition to effectively treat

an animal or human. No working examples are provided which would provide sufficient guidance to allow one skilled in the art to practice the above embodiments of the invention with a reasonable expectation of success. The claims read on in vivo treatments and prevention of HBV infection. There is a difference between in vivo and invitro methods. This is an area a great unpredictability. The following example shows the unpredictability and lack of correlation between in vivo and in vitro.

Characteristics of a compound's activity *in vitro* using purified or partially purified components generally differs significantly with the compound when used *in vivo*. Additionally, cultured cell lines generally differ significantly from *in vivo* animal models. The compound must be delivered to the target site in a sufficient concentration and for a sufficient period of time. *In vitro* assays cannot duplicate the complex conditions of *in vivo* therapy. In the *in vitro* assays, the compound is in constant contact with cells and virus. This is not the case *in vivo*, where exposure to the target may be delayed or inadequate. In addition, variables such as biological stability, half-life or clearance are important parameters in achieving successful therapy with the compound. In addition, the composition may not reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where the composition has no effect, circulation into the target area may be insufficient to carry the composition and a large enough local concentration may not be established.

An example of *in vivo* vs. *in vitro* environments that shows a lack of correlation between the two environments in the effect of an antiviral pharmaceutical composition is suramin. Mitsuya *et al.* teach that surimin can inhibit retrovirus RT in vitro at levels that

are clinically obtainable in humans (abstract). Sandstrom *et al.* teach that suramin was discontinued from clinical use due to adverse side effects and no strong showing of effective reduction of infectious virus (page 376, column 2).

Those of skill in the art recognize those *in vitro* assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlation is generally lacking. The greatly increased complexity of the *in vivo* environment as compared to the very narrowly defined and controlled conditions of an *in vitro* assay does not permit extrapolation of *in vitro* assays to animal or human efficacy with any reasonable degree of predictability.

The specification does not disclose the specific binding motif on the protein SEQ ID# 4 that binds to the known peptides.

The specification has not shown that this protein actually inhibits binding of HBV to hepatic cells. The specification infers this from the binding of SEQ ID#s 8 and 9.

It is not shown that the binding to HBV by the urine derived protein results in blocking attachment. There are no working examples that show that the purified protein will block attachment. It is known in the art that an antibody can bind virus and can prevent attachment/ infection of a cell; however, it is also known that the another antibody directed to the same protein will also bind but not block attachment and allow infection of a cell. It is not shown that the binding epitope used by this protein will result in a blockage of attachment or if binding leaves available "another side" of the virus to bind hepatic cells. There is more than one epitope on the peptides used to screen for

SEQ ID# 4. There is no showing that the epitope bound is the same as shown in the prior art (Neurath *et al.*, from IDS).

The art is not clear that there is only one receptor for HBV and there may be more (Meyer et al., from IDS page 147, last paragraph- end of 148).

The characteristics of these proteins as recited in claim 8 do not enable one to a more refined area of search to find other proteins. Disulfide bonds, glycosylation, signal sequences and other characteristics define a broad range of human proteins. These characteristics were not used to discover the claimed composition. The two disclosed isolated proteins do not share extensive homology or identity as shown on the table on page 46. A particular binding motif is not disclosed and it is not known if the same motif is used in both proteins.

It would require undue experimentation to practice the invention as claimed. No specific binding motif is taught that indicates what part of the structure is important or if it is the same in both proteins. No evidence has been provided which would allow one of skill in the art to predict the efficacy of using the recombinant protein as a pharmaceutical agent for the method of inhibiting HBV binding to hepatic cells. Therefore, the instant invention is not enabled for the broadly claimed recombinant urine derived protein comprising portions and 60% homologous proteins for inhibiting HBV binding to hepatic cells. Also, the importance of the claimed characteristics in claim 8, has not been shown to be relevant to inhibiting binding.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to the method with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed.

Claims 1- 8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The burden of the written description requirement in this application for recombinant urine derived proteins that bind an HBV preS1 peptide and inhibit the binding of HBV to hepatic cells and a whole range of nucleotide sequences that encode proteins.

The written description in this case only sets forth two proteins that bind the HBV peptide.

Vas-Cath Inc. v. Mahurkar ((CAFC, 1991) 19 USPQ2d 1111), clearly states that "Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See Vas-Cath at page 1117). The specification does not "clearly allow persons of ordinary skill in the art

to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). It is respectfully submitted that the instant specification, in fact, only sets out two proteins that bind an HBV peptide of SEQ ID# 9. Accordingly, there is evidence that the full scope of the claimed invention was not in Applicant's possession as of the filing date sought.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see Vas-Cath at page 1115).

With the exception of two proteins disclosed, the skilled artisan cannot envision all the encompassed proteins and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. The two disclosed proteins are not very related by homology and it is not disclosed what is the critical binding region or any specific showing that the protein inhibits binding of HBV to hepatic cells. Without knowing more of what is required for the composition of claim 1, the coding sequences of claim 3, parts b and c, are not fully described either. Polynucleotides that are related by percent identity or hybridization conditions allow for the alteration of too many amino acid residues to retain the binding ability to the HBV peptide especially in view of not knowing what sequence is important. Adequate written description requires more than a mere statement that it is part of the invention. See Fiers v. Revel, ((CAFC, 1993) 25 USPQ 2d 1601) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,((CAFC, 1991) 18 USPQ2d 1016).

Therefore only the recombinant urine derived protein of SEQ ID#4 is described, but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1- 8 are rejected under 35 U.S.C. 102(e) as being anticipated by Jacobs *et al.* (US 2001/0016650, published 23 August 2001, SEQ ID# 6 is found in application 08/885610, filed 30 June 1997).

Jacobs *et al.* teach a secreted protein (claim 4) that was isolated from kidneys (paragraph 0051) that is 99% identical to the claimed SEQ ID #4.

Jacobs *et al.* teach that this protein can be used as a pharmaceutical agent (paragraph 200), that it can be used to treat hepatitis (paragraph 0104), and that it contains at least a signal peptide (paragraph 0053).

Portions of both the claimed and prior art proteins share 100% identity.

Jacobs *et al.* is silent concerning if it binds to HbsAg preS1 peptide or portion, if it binds to HBV particles, and ift it binds to specific sequences.

The disclosed protein and method meet the described properties of the claimed method in that the proteins are 99% identical, thus must be able to inhibit HBV infection.

Where, as here, the Patent Office lacks the facilities to perform comparisons between the claimed material and prior art materials that reasonably appear to meet the claim limitations, the burden is properly shifted to applicant to distinguish the claimed product from the prior art product. See In re Best, Bolton, and Shaw, 195 USPQ 430 (CCPA 1977); Ex Parte Gray, 10 USPQ2nd 1922 (BPAI 1989).

Conclusion

No claim is allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Myron G. Hill whose telephone number is 571-272-0901. The examiner can normally be reached on 9am-6pm Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Myron G. Hill
Patent Examiner
December 11, 2004

JAMES HOUSEL 12/13/04
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